MICHAEL T. FASULLO, Ph.D., LOYOLA UNIVERSITY MEDICAL CENTER $35,000

Genetic Characterization of Damage-induced Recombination between Dispersed Repetitive Sequences in Saccharomyces Cerevisiae

Many leukemias are correlated with the appearance of genomic rearrangements and the exposure to ionizing radiation. These rearrangements include specific translocations and deletions, and the endpoints of some of these rearrangements reside within a small repetitive element in man, known as *Alu*. However, it is unknown whether DNA damaging agents, such as ionizing radiation, can stimulate somatic recombination between Alu sequences. The purpose of this study is to determine whether DNA damaging agents can stimulate recombination between dispersed repetitive elements using the yeast *Saccharomyces cerevisiae* as a model organism. We will then investigate whether sequence divergence between these sequences modulates this recombination and whether specific genes, such as those involved in mismatch repair and topoisomerases, are important in controlling this recombination. If these novel recombination constructs are successful, similar constructs can be made and tested in mammalian cell culture, using known mammalian genes. These studies will contribute to leukemia research by demonstrating that defects in specific DNA repair functions, such as those shown to be important in the pathogenesis of colorectal cancer, may also contribute to the formation of reciprocal translocations in yeast.

THOMAS E. SMITHGALL, Ph.D., UNIVERSITY OF NEBRASKA MEDICAL CENTER $35,000

Interaction of the FES Tyrosine Kinase with BCR and BCR/ABL

A major problem with chemotherapy for leukemia (and most other forms of cancer) is the inability of anti-cancer drugs to distinguish between normal and cancerous cells, resulting in severe toxicity that limits the dose of the drug that can be given to a patient. An alternative to this conventional cytotoxic, or cell-killing, therapy would be to use compounds that induce the leukemic cells to mature normally and stop dividing. This research proposal is designed to characterize a novel interaction between two cellular proteins that may have a direct role in mediating the responsiveness of leukemic cells to normal maturation-inducing signals. Understanding the mechanism responsible for blood cell development may ultimately form the basis for a new class of non-toxic anti-leukemic drugs.

PETER K. ROGAN, Ph.D., THE PENNSYLVANIA STATE UNIVERSITY $35,000
THE MILTON S. HERSHEY MEDICAL CENTER

Genetic Etiology of Leukemia in Down Syndrome

Children with Down syndrome develop acute leukemia of childhood much more often than normal children. In Down syndrome, individuals inherit an extra copy of chromosome 21. This chromosome probably carries mutations in one or more genes that predisposes these children to develop leukemia. This study is focused on looking for these genes. In this study, we will examine the pattern of inheritance of genetic probes on chromosome 21 in children with Down syndrome who have developed and recovered from childhood leukemia. The genetic information that we will obtain will most likely reveal the number and approximate locations of the leukemia genes on chromosome 21. Identification of the gene(s) responsible for this predisposition would have important implications for diagnosis and treatment of leukemia in this group of patients as well as a potentially profound impact upon our understanding of the pathogenesis of acute leukemia in general.